Monitoring the US Blood Supply

In recent years, there has been increasing concern about the adequacy of the US blood supply, especially as blood donor criteria become more stringent and the population ages. Multiple surveys through the years have suggested that the demand for blood and the supply were coming closer together, leaving little flexibility for emergencies, seasonal changes and blood group frequency distribution effects. These surveys were performed at varying intervals and the data could not be made available in timely fashion.

The US Department of Health and Human Services determined that the blood supply should be monitored in more timely fashion to assess the effects of donation policy changes an provide a basis for planning. The National Heart, Lung, and Blood Institute contracted with the National Blood Data Resource Center to purchase data collected monthly from a sample of blood centers and hospital transfusion services selected to be representative of the country. Sampling of blood centers began with January 2000; transfusion service sampling is expected to begin soon. Blood centers were asked to provide retrospective information back to October 1999. Data are reported to the NHLBI under code without identifying individual blood centers.

Information was to be collected by blood group and included the production (released for distribution after losses) of red cells and platelets (random donor and by apheresis), bimonthly inventories (1st and 3rd Wednesdays), imports, exports and outdates. Twenty-six centers are participating, although a few have been unable to supply data every month. Numbers were "normalized" to 26 centers to facilitate month-to-month comparisons. Most centers were unable to supply retrospective inventory information, but many were able to provide supply data.

The two charts show, respectively, RBC supply (products released, October 1999 through July 2000) and

red cell product inventories on the first and third Wednesday of each month, January 2000 through the first Wednesday in August.

Thanks are due to the participating blood centers for providing timely data and helping to determine if the US blood supply can be monitored to provide useful information.

Final August 23, 2000

D:\MyFiles\WP68\Data\Datapub82100.wpd

9-14-00 9:00 AM

OPEN Cmte Discussion

BLOOD PRODUCTS ADVISORY COMMITTEE MEETING
67th MEETING – September 14-15, 2000

TOPIC: HIV p24 antigen testing of plasma for fractionation - Potential Criteria for Discontinuation

Issue: Should FDA permit manufacturers of plasma derivatives to replace HIV p24 antigen testing with a licensed minipool NAT method that has equal or greater sensitivity ?

Background

Introduction:

During the past decade there has been a dramatic reduction in the transmission of HIV by blood and blood products primarily due to the implementation of sensitive tests for viral antibody, antigen, and nucleic acid and, in the case of plasma derivatives, the use of effective virus removal and inactivation methods for plasma derivatives. The major sources of remaining risk are window period donations, viral variants, atypical seroconversion and laboratory testing error. According to recent reports, donations during the window period constitute at least 90% of the risk. Therefore, measures to close the window period could further reduce the low residual risk in HIV transmission by blood and plasma. In 1994, FDA held a workshop to discuss the potential application of nucleic acid based methods to donor screening for HIV. It was felt at the time that although these methods were clearly sensitive, they were not ready for implementation on a large scale. It was subsequently decided in 1996 that p24 antigen (Ag) testing could be adopted as an interim measure for interdicting window period donations until more sensitive methods become available. Despite the effectiveness of viral clearance and inactivation procedures in the manufacture of plasma derivatives, FDA recommended donor testing for HIV-1 p24 antigen for plasma for fractionation as an added safeguard. Such testing limits the virus burden that may be present in a plasma pool for fractionation.

Subsequent to implementation of HIV p24 Ag testing in 1996, the industry actively pursued development of nucleic acid testing (NAT) for screening blood and plasma donors. Due to the cost and labor intensity of NAT there was much interest in testing minipools of plasma and by 1997, some manufacturers in Europe had voluntarily instituted NAT on minipools. At about that time, the European Union had issued a directive that by July 1,1999 HCV RNA testing would be required in Europe for all plasma for fractionation and that the requirement for HIV-1 RNA testing would follow at a later date. In the U.S., testing of minipools first was introduced as an in-process control test for plasma for fractionation. However, the FDA position to regard pooled sample testing by NAT as a form of donor screening and the European directive which applied to both Source and Recovered Plasma provided impetus to the rapid development of NAT for all blood and plasma donations. FDA has taken the position that all NAT tests used to

screen blood and plasma are subject to regulation as biological products under the licensing mechanism. Since NAT screening of donors was expected to improve blood safety while not interfering with current measures of safety, FDA permitted the clinical study of this investigational technology on a large scale. Such large scale studies would be necessary to demonstrate the efficacy of NAT primarily because the frequency of window period donations is low. At the present time virtually all Source Plasma and Whole Blood collected in the U.S. is being tested by a minipool NAT method for HCV and HIV-1 under an approved IND. FDA has not yet licensed a NAT method for use in screening of donor blood and plasma, including Source Plasma.

Criteria for discontinuation of HIV p24 Ag and replacement by minipool NAT

With the implementation of NAT for detection of window period donations, the question of replacing HIV p24 Ag testing by NAT has been raised by many investigators. Since both tests are for direct makers for the virus, it has been suggested that it may be feasible to replace p24 Ag on the neat sample with minipool NAT if it is found to be of equal or greater sensitivity. At the Blood Products Advisory Committee (BPAC) meeting held in March 1999, FDA defined criteria for discontinuation of HIV p24 Ag and replacement by minipool NAT. To summarize briefly, the following criteria were presented:

a. The sensitivity of the NAT method should be equal to or greater than that of p24 Ag testing for the window period. This could be established by testing all available and properly stored repository specimens that are p24 Ag positive and antibody negative and commercially available serconversion panel specimens in the pooled NAT method and neat p24 Ag method.

b. The frequencies of NAT and p24 Ag positivity in Ab positive and negative specimens should be evaluated in prospective studies.

c. NAT and p24 Ag should have equivalent sensitivity for the major HIV-1 subtypes. NAT should detect all variant subtypes detected by p24 Ag tests.

d. Weakly reactive p24 Ag positive specimens should be reproducibly detected by the NAT method on multiple days by multiple operators and for multiple kit lots, and instruments

FDA also indicated that the NAT method would have to be licensed before it could be used to replace the antigen test. FDA has published guidance on the validation of NAT methods to screen plasma donors. Among the major considerations for the sensitivity of NAT on pools is the analytical sensitivity of the NAT method on the pool and the original donation, as well as the pool size tested. FDA has defined a proposed sensitivity limit of 100 copies/ml for the pool test and 5,000 copies/ml for the original donation. FDA has not specified pool size limits, thereby allowing manufacturers to set these limits based on the analytical sensitivity of their specific test. Source Plasma donations are currently being tested in pools ranging from 96 to 1200 donations.

To establish sensitivity criteria whereby p24 Ag can be discontinued, it is important to understand the early dynamics of HIV infection and to establish a relationship between detectable levels of viremia by p24 Ag vs. minipool NAT. Recent data indicate, that in studies where 146 serial specimens from 43 HIV plasma donor panels were characterized by tests for HIV RNA , p24 Ag and HIV Ab, the viral load at the time of p24 antigen seroconversion was estimated at 10,000 copies/ml (CI = 1,000 – 100,000). Therefore a NAT method should be able to detect a minimum of 10,000 copies/ml in order to replace currently licensed p24 Ag tests. For example, if a NAT method has a test sensitivity of 100 copies/ml the maximum pool dilution where p24 antigen and NAT would be expected to have equal sensitivity is 100 samples/pool. However, if a test has a higher analytical sensitivity e.g. 10 copies/ml, it is conceivable that a pool size of 1,000 would also permit equal sensitivity of NAT and p24.

In regard to plasma for further manufacture, it is important to note that viral inactivation methods provide an added measure of safety. Since the end of 1987 there have been no transmissions of HIV by albumins, immuneglobulins , AHF or F IX. Heat treatment used in albumin production can inactivate the infectivity of HIV-1 by at least 7 logs which is three logs more virus than the maximum concentration reported in the plasma of infected individuals (10^4 infectious doses/ml). The Cohn-Oncley method used to manufacture immuneglobulins can remove greater than 10^{15} infectious doses of HIV per ml which is at least 11 logs greater than the maximum circulating infectious doses per ml. Finally, there have been no seroconversions to anti-HIV among hemophiliacs who have received AHF or F IX manufactured from screened plasma and that has been virally inactivated.

Based on the rationale and criteria outlined above, the FDA is seeking the recommendations of the BPAC on the potential discontinuation of HIV p24 antigen testing and replacement by a NAT method for plasma collected for fractionation. As outlined above, the two major considerations are: a) that a NAT test is of equal or greater sensitivity than the p24 Ag test, and b) that viral removal/inactivation methods validated to remove/inactivate circulating levels of HIV detected by p24 or NAT are in place for plasma collected for further manufacturing.

Questions for the Committee:

1. Do the Committee members agree that HIV-1 p24 antigen testing of Source Plasma may be discontinued if:

   a) It is demonstrated that a particular licensed NAT method can detect HIV at a level of 5,000 copies/ml or less in a unit of plasma, even if the donor sample is tested as part of a pool, and
   b) Comparative studies of the NAT method vs. HIV-1 p24 are consistent with the hypothesis that the NAT method is of equal or greater sensitivity (including the ability to detect major subtypes) ?

2. If committee members disagree, please comment on an appropriate alternative.

I. A.

Criteria for Discontinuation of HIV-1 p24 Antigen Screening of Source Plasma: Current Thinking

BACKGROUND

When HIV-1 p24 antigen testing was instituted in March, 1996, for the screening of blood and plasma donors, it was recognized that antigen tests were less sensitive than nucleic acid tests (NAT), particularly NAT for viral RNA. Based on seroconversion data, it was estimated that NAT could eventually reduce the window period for HIV by an additional 5 days (from 16 days to 11 days) over the reduction achieved by antigen testing when compared with detection of antibodies determined using the most sensitive antibody tests (i.e. from 22 days to 16 days). However, NAT was only feasible at the time in a research setting, and it was decided to adopt p24 antigen testing as an interim measure for interdicting window period donations.

Since the initiation of antigen testing over four years ago, according to data from the American Red Cross, a total of 10 window period units have been detected by HIV antigen testing alone in the U.S. and Puerto Rico. In HIV infection p24 antigen and viral RNA are direct viral markers which display similar patterns in the early window phase of infection. With the implementation under IND of NAT testing of U.S. donors of Whole Blood and Source Plasma using pooled donor plasma which has been sparked by European requirements, the feasibility of replacing HIV-1 p24 antigen testing with NAT testing for early detection of window period donations has been raised by many in the field..

FDA's current thinking

At the BPAC meeting held on March 25, 1999, FDA announced its thinking on the issue of criteria for replacement of p24 with NAT. These and a few additional points that were added subsequent to the BPAC meeting are outlined below. An applicant would be required to submit the following data to justify replacing p24 antigen testing with NAT minipool testing or with NAT testing of individual plasma donations:

1. Data showing that the sensitivity of the NAT test is equal to or greater than that of p24 antigen testing in the window period.

    a) NAT testing must be able to detect all available repository p24-positive antibody-negative window period blood donation specimens detected since the start of p24 screening when those specimens are included in a plasma pool. (whether or not they remain p24-positive when diluted in the pool) or

when tested individually.

b) Data showing that NAT testing can detect p24-positive samples in commercial plasma donor seroconversion panels when tested individually or with adequate sensitivity to address the dilution factor due to pooling (i.e., when those samples are diluted in a plasma pool).

c) Data from clinical trials comparing the relative frequencies of detection for antigen testing and NAT testing in prospective studies of Whole Blood and plasma populations. The number of p24-positive or NAT-positive window period units required would be established prior to such clinical trials by statistical evaluation and agreed to by FDA. This prospective data will include analysis of the NAT-positive rate for p24-positive antibody-positive as well as p24-positive antibody-negative specimens.

2. Data showing that NAT testing is able to detect all HIV variants (including HIV-1 group M subtypes A through G and group O) that would be detected by the licensed p24 antigen tests. This can be provided by testing well-characterized p24-positive antibody-positive samples from HIV-1 variants (10 of each HIV-1 group M subtype A-G). A combination of naturally-occurring human serum samples and cell culture fluids from HIV-1 variants spiked into normal plasma should be used to demonstrate the sensitivities of the p24 assay and the NAT test. FDA may work with industry to identify and collect such specimens and establish a validation panel.

3. Data from reproducibility studies of the NAT testing method in routine operational settings to demonstrate that even weakly reactive p24 antigen samples will be detected by the NAT test on multiple days, instrument systems, operators, and product lots.

4. The NAT testing method must be licensed by FDA. (NAT testing under IND will not be allowed to replace p24 antigen testing).

5. A testing organization must submit an IND or amend an existing IND that outlines specific clinical trials to substantiate a claim of replacing HIV p24 antigen testing with NAT testing. Because of differences in NAT methods and INDs, licensure of NAT testing with a substantiated claim for replacement of p24 antigen testing for a specific testing organization will form the basis for discontinuation of p24 antigen testing by that organization using the licensed NAT method. This approach will be adopted rather than an industry-wide withdrawal of p24 antigen testing recommendations by FDA.

I. B.